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1: J Inherit Metab Dis. 2001;24 Suppl 2:47-51; discussion 45-6. Related Articles, Links

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Variable clinical presentation in lysosomal storage disorders.

Beck M.

Children's Hospital, University of Mainz, Germany. Beck@kinder.klinik.uni-mainz.de

Extensive clinical heterogeneity is seen in lysosomal storage disorders, regarding the age of onset and severity of symptoms, the organs involved, and effects on the central nervous system. A broad phenotypic spectrum is seen, for example, in mucopolysaccharidosis type I (Hurler/Scheie disease), Gaucher disease, the several forms of GM2-gangliosidosis and the different manifestations of beta-galactosidase deficiency (GM1-gangliosidosis and Morquio disease type B). Variable clinical expression of the same enzyme defect is not well understood. The presence of different mutations is only part of the explanation, as intrafamilial variability is observed in many cases. Other mechanisms, for example the effect of specific activators, may also have an influence on phenotype.

Publication Types:
- Review
- Review, Tutorial

PMID: 11758678 [PubMed - indexed for MEDLINE]

2: Chem Rev. 2000 Dec 13;100(12):4683-96. Related Articles, Links

ACS PUBLICATIONS

Inhibition of glycosphingolipid biosynthesis: application to lysosomal storage disorders.

Butters TD, Dwek RA, Platt FM.

Oxford Glycobiology Institute, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, U.K.

PMID: 11749362 [PubMed - as supplied by publisher]

3: Expert Opin Biol Ther. 2001 Sep;1(5):857-67. Related Articles, Links

Full text article at www.ashley-pub.com

Gene therapy for lysosomal storage disorders.

Barranger JM, Novelli EA.

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The lysosomal storage disorders (LSD) are monogenic inborn errors of metabolism with heterogeneous pathophysiology and clinical manifestations. In the last decades, these disorders have been models for the development of molecular and cellular therapies for inherited metabolic diseases. Studies in preclinical in vitro systems and animal models have allowed the successful development of bone marrow transplantation (BMT) and enzyme replacement therapy (ERT) as therapeutic options for several LSDs. However, BMT is limited by poor donor availability and high morbidity and mortality, and ERT is not a life-long cure. Moreover, the neuropathology present in many LSDs responded poorly, if at all, to these treatments. Therefore, gene therapy is an attractive therapeutic alternative. Gene therapy strategies for LSDs have employed ex vivo gene transduction of cellular targets with subsequent transplantation of the enzymatically corrected cells, or direct in vivo delivery of the viral vectors. Oncoretroviral vectors and more recently adeno associated vectors (AAV) and lentiviral vectors have been extensively tested, with some success. This review summarises the main gene therapy strategies which have been employed or are under development for both non-neurological and neuronopathic LSDs. Some of the in vitro and in vivo preclinical studies presented herein have provided the rationale for a gene therapy clinical trial for Gaucher disease Type I.

Publication Types:
- Review
- Review, Tutorial

PMID: 11728220 [PubMed - indexed for MEDLINE]

4: Eur J Paediatr Neurol. 2001;5 Suppl A:73-9. Related Articles, Links

Tripeptidyl-peptidase I in neuronal ceroid lipofuscinoses and other lysosomal storage disorders.

Wisniewski KE, Kida E, Walus M, Wujek P, Kaczmarski W, Golabek AA.

Department of Pathological Neurobiology, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, NY 10314, USA.

The classic late infantile form of neuronal ceroid lipofuscinosis (CLN2, cLINCL) is associated with mutations in the gene encoding tripeptidyl-peptidase I (TPP-I), a lysosomal aminopeptidase that cleaves off tripeptides from the free N-termini of oligopeptides. To date over 30 different mutations and 14 polymorphisms associated with CLN2 disease process have been identified. In the present study, we analysed the molecular basis of 15

different mutations of TPP-I by using immunocytochemistry, immunofluorescence, Western blotting, enzymatic assay and subcellular fractionation. In addition, we studied the expression of TPP-I in other lysosomal storage disorders such as CLN1, CLN3, muccopolysaccharidoses and GM1 and GM2 gangliosidoses. Our study shows that TPP-I is absent or appears in very small amounts not only in cLINCL subjects with mutations producing severely truncated protein, but also in individuals with missense point mutations, which correlates with loss of TPP-I activity. Of interest, small amounts of TPP-I were detected in lysosomal fraction from fibroblasts from cLINCL subject with protracted form. This observation suggests that the presence of small amounts of TPP-I in lysosomes is able to delay significantly CLN2 disease process. We also show that TPP-I immunoreactivity is increased in the brain tissue of CLN1 and CLN3 subjects, stronger in glial cells and macrophages than neurons. Less prominent increase of TPP-I staining was found in muccopolysaccharidoses and GM1 and GM2 gangliosidoses. These data suggest that TPP-I participates in lysosomal turnover of proteins in pathological conditions associated with cell/tissue injury.

PMID: 11589013 [PubMed - indexed for MEDLINE]

☐ **5:** Ment Retard Dev Disabil Res Rev. 2001;7(3):190-9. Related Articles, Links

Systematic approach to the diagnosis of lysosomal storage disorders.

Weibel TD, Brady RO.

Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892-1260, USA.

Disorders that arise as a result of lysosomal dysfunction represent some of the most challenging diagnostic problems in medicine. Not only are these disorders infrequently seen, but they may also present with signs and symptoms that mimic perinatal injury, food intolerance, or the sequellae of neonatal infection. Misidentification can lead to significant delay in diagnosis. Ironically, as the prevailing economic climate places increasing time constraints on practicing physicians, medical research is providing treatment strategies and management techniques that are most effective if applied early in the course of the disease. Most lysosomal storage disorders can now be definitively diagnosed once the signs are recognized. In many cases the benefits of early diagnosis, enlightened management, and appropriate referral are considerable. The aim of this paper is to demystify this elusive class of diseases, to promote clinical vigilance in their detection, and to provide a systematic approach to diagnosis when clinical suspicion is aroused. Copyright 2001 Wiley-Liss, Inc.

Publication Types:
- Review
- Review, Tutorial

PMID: 11553935 [PubMed - indexed for MEDLINE]

☐ **6:** Curr Opin Mol Ther. 2001 Aug;3(4):399-406. Related Articles, Links

Gene therapy for lysosomal storage disorders.

Yew NS, Cheng SH.

Genzyme Corporation, Framingham, MA 01701-9322, USA. nelson.yew@genzyme.com

Deficiencies in one or several of the numerous degradative enzymes that reside in the lysosome often result in one of many clinically severe diseases, almost all of which have no currently available therapy. Although bone marrow transplantation, enzyme replacement and substrate inhibition therapies are being considered, gene therapy represents an increasingly attractive approach, particularly for those lysosomal storage diseases with neurological manifestations. This review summarizes the most recent advances in developing gene therapies for this large and heterogeneous group of disorders.

Publication Types:
- Review
- Review, Tutorial

PMID: 11525564 [PubMed - indexed for MEDLINE]

7: Southeast Asian J Trop Med Public Health. 1999;30 Suppl 2:111-3. Related Articles, Links

Pilot neonatal screening program for lysosomal storage disorders, using lamp-1.

Ranierri E, Gerace RL, Ravenscroft EM, Hopwood JJ, Meikle PJ.

Department of Chemical Pathology, Women's and Children's Hospital, North Adelaide, Australia.

We have demonstrated that the lysosome associated membrane protein (LAMP-1) is elevated in plasma from approximately 70% of lysosomal storage disorder patients. As part of the development of a newborn screening program for lysosomal storage disorders we have developed a first tier screening assay based upon the level of LAMP-I in blood spots taken from newborn Guthrie cards. To determine the effectiveness of the first-tier marker a prospective pilot Guthrie neonatal screening program for the identification of LSD was commenced in April 1998. Prior to commencement of the pilot program ethical approval was obtained and information leaflets regarding the neonatal screening of LSD were distributed to parents at the time of their infant's Guthrie collection. The LAMP-1 assay utilizes a chicken polyclonal and a mouse monoclonal in a sandwich time resolved fluorescent immunoassay. LAMP-1 blood-spot calibrators and quality control specimens were developed and shown to be stable and reproducible. To date 11,183 infants have been screened using LAMP-1. The population distribution is described with a median and 98th percentile of 220pg/l whole blood and 483microg/l whole blood respectively. Acceptable CV% for intra and inter assay of 8.9% and 10% respectively were obtained.

PMID: 11400745 [PubMed - indexed for MEDLINE]

8: Southeast Asian J Trop Med Public Health. 1999;30 Suppl 2:104-10. Related Articles, Links

Newborn screening for lysosomal storage disorders.

Meikle PJ, Ranieri E, Ravenscroft EM, Hua CT, Brooks DA, Hopwood JJ.

Department of Chemical Pathology, Women's and Children's Hospital, North Adelaide, Australia. pmeikle@medicine.adelaide.edu.au

Lysosomal storage disorders (LSD) represent a group of over 40 distinct genetic diseases with a total incidence of approximately 1:7,000 births. Bone marrow transplantation and enzyme replacement therapy are currently in use for the treatment of some disorders and new forms of enzyme and gene replacement therapy are actively being researched. The effectiveness of these therapies, particularly for the LSD involving the central nervous system and bone pathology, will rely heavily upon the early diagnosis and treatment of the disorder, before the onset of irreversible pathology. In the absence of a family history the only practical way to detect these disorders will be by a newborn screening program. One common feature of these disorders is an increase in the number and size of lysosomes within the cell from approximately 1% to as much as 50% of total cellular volume. Associated with this, is a corresponding increase in some lysosomal proteins. We propose that the measurement of one or more of these proteins in blood spots taken from Guthrie cards, will form the basis of a newborn screening program, for the detection of all LSD. We have identified a number of lysosomal proteins as potential markers for LSD. The level of these proteins has been determined in blood spots taken from Guthrie cards and in plasma samples from over 300 LSD affected individuals representing 25 disorders. Based on these results we have proposed a strategy for a newborn screening program involving a two tier system, utilizing time resolved fluorescence immunoquantification of the protein markers in the first tier, followed by tandem mass spectrometry for the determination of stored substrates in the second tier assays.

PMID: 11400743 [PubMed - indexed for MEDLINE]

9: Clin Chem. 2000 Sep;46(9):1318-25. Related Articles, Links

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Determination of acid alpha-glucosidase protein: evaluation as a screening marker for Pompe disease and other lysosomal storage disorders.

Umapathysivam K, Whittle AM, Ranieri E, Bindloss C, Ravenscroft EM, van Diggelen OP, Hopwood JJ, Meikle PJ.

Lysosomal Diseases Research Unit and State Screening Services, Department of Chemical Pathology, Women's and Children's Hospital, 72 King William Rd., North Adelaide, South Australia 5006, Australia.

BACKGROUND: In recent years, there have been significant advances in the development of enzyme replacement and other therapies for lysosomal storage disorders (LSDs). Early diagnosis, before the onset of irreversible pathology, has been demonstrated to be critical for maximum efficacy of current and proposed therapies. In the absence of a family history, the presymptomatic detection of these disorders ideally can be achieved through a newborn screening program. One approach to the development of such a program is the identification

of suitable screening markers. In this study, the acid alpha-glucosidase protein was evaluated as a marker protein for Pompe disease and potentially for other LSDs. METHODS: Two sensitive immunoquantification assays for the measurement of total (precursor and mature) and mature forms of acid alpha-glucosidase protein were used to determine the concentrations in plasma and dried blood spots from control and LSD-affected individuals. RESULTS: In the majority of LSDs, no significant increases above control values were observed. However, individuals with Pompe disease showed a marked decrease in acid alpha-glucosidase protein in both plasma and whole blood compared with unaffected controls. For plasma samples, this assay gave a sensitivity of 95% with a specificity of 100%. For blood spot samples, the sensitivity was 82% with a specificity of 100%. CONCLUSIONS: This study demonstrates that it is possible to screen for Pompe disease by screening the concentration of total acid alpha-glucosidase in plasma or dried blood spots.

PMID: 10973860 [PubMed - indexed for MEDLINE]

10: J Am Soc Nephrol. 2000 Aug;11(8):1542-7. Related Articles, Links

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Gene therapy for lysosomal storage disorders with neuropathology.

Ioannou YA.

Department of Human Genetics, Gene Therapy and Molecular Medicine, The Mount Sinai School of Medicine, New York, NY 10029-6574, USA. ioanny01@doc.mssm.edu

Publication Types:
- Review
- Review, Tutorial

PMID: 10906169 [PubMed - indexed for MEDLINE]

11: Clin Chem. 2000 Feb;46(2):167-74. Related Articles, Links

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Saposins A, B, C, and D in plasma of patients with lysosomal storage disorders.

Chang MH, Bindloss CA, Grabowski GA, Qi X, Winchester B, Hopwood JJ, Meikle PJ.

Lysosomal Diseases Research Unit, Department of Chemical Pathology, Women's and Children's Hospital, 72 King William Road, North Adelaide, South Australia 5006, Australia.

BACKGROUND: Early diagnosis of lysosomal storage disorders (LSDs), before the onset of irreversible pathology, will be critical for maximum efficacy of many current and proposed therapies. To search for potential markers of LSDs, we measured saposins A, B, C, and D in patients with these disorders. METHODS: Four time-delayed fluorescence

immunoquantification assays were used to measure each of the saposins in plasma from 111 unaffected individuals and 334 LSD-affected individuals, representing 28 different disorders. RESULTS: Saposin A was increased above the 95th centile of the control population in 59% of LSD patients; saposins B, C, and D were increased in 25%, 61%, and 57%, respectively. Saposins were increased in patients from several LSD groups that in previous studies did not show an increase of lysosome-associated membrane protein-1 (LAMP-1). CONCLUSION: Saposins may be useful markers for LSDs when used in conjunction with LAMP-1.

PMID: 10657372 [PubMed - indexed for MEDLINE]

12: Adv Pediatr. 1999;46:409-40. Related Articles, Links

Hydrops fetalis: lysosomal storage disorders in extremis.

Stone DL, Sidransky E.

Clinical Neuroscience Branch, National Institute of Mental Health, Bethesda, Maryland, USA.

In recent years there has been an increased recognition that hydrops fetalis may be an extreme presentation of many of the lysosomal storage disorders. Hydrops fetalis, the excessive accumulation of serous fluid in the subcutaneous tissues and serous cavities of the fetus, has many possible etiologies, providing a diagnostic challenge for the physician. Ten different lysosomal storage disorders have now been diagnosed in infants with hydrops fetalis, including mucopolysaccharidosis (MPS) VII and IVA, type 2 Gaucher disease, sialidosis, GMI gangliosidosis, galactosialidosis, Niemann-Pick disease type C, disseminated lipogranulomatosis (Farber disease), infantile free sialic acid storage disease (ISSD), and mucolipidosis II (I-cell disease). Frequently, these inborn errors of metabolism are recognized only after the unfortunate recurrence of hydrops fetalis in several pregnancies of a family. Making the diagnosis relies on the physician having a high index of suspicion and ordering appropriate testing, which can often be performed prenatally. In several of these disorders, including MPS VII, infantile galactosialidosis, type 2 Gaucher disease, and ISSD, hydrops fetalis is a relatively common presentation. A greater physician awareness of hydrops fetalis as a presentation of lysosomal disease will facilitate establishing a diagnosis in cases that would have previously been considered idiopathic and will enable a better estimation of the incidence of this association. Lysosomal disorders are among the few causes of nonimmune hydrops fetalis in which an accurate recurrence risk can be ascertained. With an early and accurate diagnosis, genetic counseling and family planning can be offered in these difficult cases.

Publication Types:
- Review
- Review, Tutorial

PMID: 10645471 [PubMed - indexed for MEDLINE]

13: Pediatr Res. 1999 Nov;46(5):501-9. Related Articles, Links

Alpha-mannosidosis in the guinea pig: a new animal model for lysosomal storage disorders.

Crawley AC, Jones MZ, Bonning LE, Finnie JW, Hopwood JJ.

Department of Chemical Pathology, Women's and Children's Hospital, North Adelaide, SA, Australia.

Alpha-mannosidosis is a lysosomal storage disorder resulting from deficient activity of lysosomal alpha-mannosidase. It has been described previously in humans, cattle, and cats, and is characterized in all of these species principally by neuronal storage leading to progressive mental deterioration. Two guinea pigs with stunted growth, progressive mental dullness, behavioral abnormalities, and abnormal posture and gait, showed a deficiency of acidic alpha-mannosidase activity in leukocytes, plasma, fibroblasts, and whole liver extracts. Fractionation of liver demonstrated a deficiency of lysosomal (acidic) alpha-mannosidase activity. Thin layer chromatography of urine and tissue extracts confirmed the diagnosis by demonstrating a pattern of excreted and stored oligosaccharides almost identical to that of urine from a human alpha-mannosidosis patient. Widespread neuronal vacuolation was observed throughout the CNS, including the cerebral cortex, hippocampus, thalamus, cerebellum, midbrain, pons, medulla, and the dorsal and ventral horns of the spinal cord. Lysosomal vacuolation also occurred in many other visceral tissues and was particularly severe in pancreas, thyroid, epididymis, and peripheral ganglion. Axonal spheroids were observed in some brain regions, but gliosis and demyelination were not observed. Ultrastructurally, most vacuoles in both the CNS and visceral tissues were lucent or contained fine fibrillar or flocculent material. Rare large neurons in the cerebral cortex contained fine membranous structures. Skeletal abnormalities were very mild. Alpha-mannosidosis in the guinea pig closely resembles the human disease and will provide a convenient model for investigation of new therapeutic strategies for neuronal storage diseases, such as enzyme replacement and gene replacement therapies.

PMID: 10541310 [PubMed - indexed for MEDLINE]

14: Biochim Biophys Acta. 1999 Oct 8;1455(2-3):69-84. Related Articles, Links

Glycoprotein lysosomal storage disorders: alpha- and beta-mannosidosis, fucosidosis and alpha-N-acetylgalactosaminidase deficiency.

Michalski JC, Klein A.

Laboratoire de Chimie Biologique, UMR 8576 CNRS (UMR 111 CNRS), Universite des Sciences et Technologies de Lille, Villeneuve d'Ascq, France. jean-claude.michalski@univ-lille1.fr

Glycoproteinoses belong to the lysosomal storage disorders group. The common feature of these diseases is the deficiency of a lysosomal protein that is part of glycan catabolism. Most of the lysosomal enzymes involved in the hydrolysis of glycoprotein carbohydrate chains are exo-glycosidases, which stepwise remove terminal monosaccharides. Thus, the deficiency of a single enzyme causes the blockage of the entire pathway and induces a storage of incompletely degraded substances inside the lysosome. Different mutations may be observed in a single disease and in all cases account for the nonexpression of lysosomal glycosidase activity. Different clinical phenotypes generally characterize a specific disorder,

which rather must be described as a continuum in severity, suggesting that other biochemical or environmental factors influence the course of the disease. This review provides details on clinical features, genotype-phenotype correlations, enzymology and biochemical storage of four human glycoprotein lysosomal storage disorders, respectively alpha- and beta-mannosidosis, fucosidosis and alpha-N-acetylgalactosaminidase deficiency. Moreover, several animal disorders of glycoprotein metabolism have been found and constitute valuable models for the understanding of their human counterparts.

Publication Types:
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- Review, Tutorial

PMID: 10571005 [PubMed - indexed for MEDLINE]

15: Exp Mol Pathol. 1999 Jun;66(2):123-30. Related Articles, Links

Comment in:
- Exp Mol Pathol. 2001 Apr;70(2):173-4.

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Molecular characterization of a novel endonuclease (Xib) and possible involvement in lysosomal glycogen storage disorders.

Malferrari G, Mazza U, Tresoldi C, Rovida E, Nissim M, Mirabella M, Servidei S, Biunno I.

Istituto Tecnologie Biomediche Avanzate-Consiglio Nazionale delle Ricerche, Via Fratelli Cervi 93, Segrate Milano, 20090, Italy.

We cloned and partially characterized a human endonuclease (Xib) which shows sequence homologies to pancreatic DNase I but an enzymatic activity closer to DNase II. We report on the structural differences found between Xib and other recently cloned human DNases. Fluores cence microscopy analysis of transiently transfected cells with Xib::pEGFP constructs indicate that the protein is located in the cytoplasm and possibly anchored to a membrane, as deduced from a hydrophobic amino acid stretch present at the C-terminal end. Xib is overexpressed in muscle and cardiac tissues and is alternately spliced in several normal and neoplastic cells. In situ hybridization studies using human cardiac and muscle biopsies indicate accumulation of Xib transcript in the vacuoles of muscle cells from patients affected by vacuolar myopathy as acid maltase deficiency; however, no point mutations were detected in their DNA. Copyright 1999 Academic Press.

PMID: 10409440 [PubMed - indexed for MEDLINE]

16: Neurochem Res. 1999 Apr;24(4):601-15. Related Articles, Links

Gene transfer approaches to the lysosomal storage disorders.

Barranger JA, Rice EO, Swaney WP.

Human Genetics Department at the University of Pittsburgh, PA 15261, USA.

The work summarized in this paper used animal and cell culture models systems to develop gene therapy approaches for the lysosomal storage disorders. The results have provided the scientific basis for a clinical trial of gene transfer to hematopoietic stem cells (HSC) in Gaucher disease which is now in progress. The clinical experiment is providing evidence of HSC transduction, competitive engraftment of genetically corrected HSC, expression of the GC transgene, and the suggestion of a clinical response. In this paper we will review the progress made in Gaucher disease and include how gene transfer might be studied in other lysosomal storage disorders.

Publication Types:
- Review
- Review, Tutorial

PMID: 10227692 [PubMed - indexed for MEDLINE]

☐ **17:** JAMA. 1999 Jan 20;281(3):249-54. Related Articles, Links

JAMA

Prevalence of lysosomal storage disorders.

Meikle PJ, Hopwood JJ, Clague AE, Carey WF.

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CONTEXT: Lysosomal storage disorders represent a group of at least 41 genetically distinct, biochemically related, inherited diseases. Individually, these disorders are considered rare, although high prevalence values have been reported in some populations. These disorders are devastating for individuals and their families and result in considerable use of resources from health care systems; however, the magnitude of the problem is not well defined. To date, no comprehensive study has been performed on the prevalence of these disorders as a group. OBJECTIVE: To determine the prevalence of lysosomal storage disorders individually and as a group in the Australian population. DESIGN: Retrospective case studies. SETTING: Australia, from January 1, 1980, through December 31, 1996. MAIN OUTCOME MEASURE: Enzymatic diagnosis of a lysosomal storage disorder. RESULTS: Twenty-seven different lysosomal storage disorders were diagnosed in 545 individuals. The prevalence ranged from 1 per 57000 live births for Gaucher disease to 1 per 4.2 million live births for sialidosis. Eighteen of 27 disorders had more than 10 diagnosed cases. As a group of disorders, the combined prevalence was 1 per 7700 live births. There was no significant increase in the rate of either clinical diagnoses or prenatal diagnoses of lysosomal storage disorders during the study period. CONCLUSIONS: Individually, lysosomal storage disorders are rare genetic diseases. However, as a group, they are relatively common and represent an important health problem in Australia.

PMID: 9918480 [PubMed - indexed for MEDLINE]

☐ **18:** FEBS Lett. 1998 Dec 28;441(3):369-72. Related Articles, Links

ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Application of magnetic chromatography to the isolation of lysosomes from fibroblasts of patients with lysosomal storage disorders.

Diettrich O, Mills K, Johnson AW, Hasilik A, Winchester BG.

Institute of Child Health, London, UK. o.diettrich@ich.ucl.ac.uk

A method for the purification of lysosomes from fibroblasts has been developed which uses endocytosis of superparamagnetic colloidal iron dextran particles followed by separation of the iron-containing lysosomes in a magnetic field. This permitted isolation of lysosomes from fibroblasts from patients with infantile sialic acid storage disorder and other lysosomal storage diseases in which a shift in lysosomal density induced by the storage material prevents purification by centrifugation in a Percoll gradient. The magnetic lysosomes isolated from these cells are very similar to those from normal cells as judged by lysosomal marker enzyme activity and 2D-PAGE analysis of the enriched proteins.

PMID: 9891973 [PubMed - indexed for MEDLINE]

19: Clin Chem. 1998 Oct;44(10):2094-102. Related Articles, Links

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Evaluation of the lysosome-associated membrane protein LAMP-2 as a marker for lysosomal storage disorders.

Hua CT, Hopwood JJ, Carlsson SR, Harris RJ, Meikle PJ.

Department of Chemical Pathology, Women's and Children's Hospital, North Adelaide, South Australia, Australia.

For many lysosomal storage disorders, presymptomatic detection, before the onset of irreversible pathology, will greatly improve the efficacy of current and proposed therapies. In the absence of a family history, presymptomatic detection can be achieved only by a comprehensive newborn screening program. Recently we reported that the lysosome-associated membrane protein LAMP-1 was increased in the plasma from approximately 70% of individuals with lysosomal storage disorders. Here we report on the evaluation of a second lysosome-associated membrane protein, LAMP-2, as a marker for this group of disorders. The median concentration of LAMP-2 in the plasma of healthy individuals was 1.21 mg/L, fourfold higher than the median LAMP-1 concentration (0.31 mg/L). LAMP-2 was increased in >66% of patients with lysosomal storage disorders, and the increases coincided with increased LAMP-1 concentrations. The reference intervals for LAMP-1 and LAMP-2 in blood spots taken from newborns were 0.20-0.54 mg/L (n = 1600) and 0.95-3.06 mg/L (n = 1600), respectively. A high correlation was observed between the concentrations of LAMP-1 and LAMP-2 in both control and affected individuals. The higher concentrations of LAMP-2, relative to LAMP-1, in plasma make LAMP-2 an attractive marker; however, the final selection will be dependent on the availability of new diagnostic markers and their ability to detect disorders currently not identified by LAMP-2.

PMID: 9761240 [PubMed - indexed for MEDLINE]

20: Ryoikibetsu Shokogun Shirizu. 1998;(19 Pt 2):601-5. Related Articles, Links

[Lysosomal transport disorders: cystinosis and sialic acid storage disorders]

[Article in Japanese]

Eto Y.

Department of Pediatrics, Tokyo Jikei University School of Medicine.

Publication Types:
- Review
- Review, Tutorial

PMID: 9645145 [PubMed - indexed for MEDLINE]

21: Brain Pathol. 1998 Jan;8(1):175-93. Related Articles, Links

Cellular pathology of lysosomal storage disorders.

Walkley SU.

Department of Neuroscience, Rose F. Kennedy Center for Research in Mental Retardation and Human Development, Albert Einstein College of Medicine, Bronx, NY 10461, USA. walkley@aecom.yu.edu

Lysosomal storage disorders are rare, inborn errors of metabolism characterized by intralysosomal accumulation of unmetabolized compounds. The brain is commonly a central focus of the disease process and children and animals affected by these disorders often exhibit progressively severe neurological abnormalities. Although most storage diseases result from loss of activity of a single enzyme responsible for a single catabolic step in a single organelle, the lysosome, the overall features of the resulting disease belies this simple beginning. These are enormously complex disorders with metabolic and functional consequences that go far beyond the lysosome and impact both soma-dendritic and axonal domains of neurons in highly neuron type-specific ways. Cellular pathological changes include growth of ectopic dendrites and new synaptic connections and formation of enlargements in axons far distant from the lysosomal defect. Other storage diseases exhibit neuron death, also occurring in a cell-selective manner. The functional links between known molecular genetic and enzyme defects and changes in neuronal integrity remain largely unknown. Future studies on the biology of lysosomal storage diseases affecting the brain can be anticipated to provide insights not only into these pathogenic mechanisms, but also into the role of lysosomes and related organelles in normal neuron function.

Publication Types:
- Review
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PMID: 9458175 [PubMed - indexed for MEDLINE]

22: Clin Chem. 1997 Aug;43(8 Pt 1):1325-35. Related Articles, Links

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Diagnosis of lysosomal storage disorders: evaluation of lysosome-associated membrane protein LAMP-1 as a diagnostic marker.

Meikle PJ, Brooks DA, Ravenscroft EM, Yan M, Williams RE, Jaunzems AE, Chataway TK, Karageorgos LE, Davey RC, Boulter CD, Carlsson SR, Hopwood JJ.

Department of Chemical Pathology, Women's and Children's Hospital, North Adelaide, Australia. omeikle@medicine.adelaide.edu.au

Early diagnosis of lysosomal storage disorders (LSDs), before the onset of irreversible pathologies, will be a key factor in the development of effective therapies for many of these disorders. Newborn screening offers a potential mechanism for the early detection of these disorders. From studies of both normal and LSD-affected human skin fibroblasts we identified the lysosome-associated membrane protein LAMP-1 as a potential diagnostic marker. We have developed a sensitive method for the quantification of this protein with a time-resolved fluorescence immunoassay. A soluble form of LAMP-1 was observed in plasma samples, and determination of 152 unaffected individuals gave a median value of 303 micrograms/L with the 5th and 95th percentile at 175 and 448 micrograms/L respectively. Plasma samples from 320 LSD-affected individuals representing 25 different disorders were assayed. We observed that 17 of the 25 disorder groups tested had > 88% of individuals above the 95th percentile of the control population, with 12 groups having 100% above the 95th percentile. Overall, 72% of patients had LAMP-1 concentrations above the 95th percentile of the unpartitioned control population. We suggest that LAMP-1 may be a useful marker in newborn screening for LSDs.

PMID: 9267309 [PubMed - indexed for MEDLINE]

23: Exp Cell Res. 1997 Jul 10;234(1):85-97. Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Lysosomal biogenesis in lysosomal storage disorders.

Karageorgos LE, Isaac EL, Brooks DA, Ravenscroft EM, Davey R, Hopwood JJ, Meikle PJ.

Department of Chemical Pathology, Women's and Children's Hospital, North Adelaide, South Australia.

Lysosomal biogenesis is an orchestration of the structural and functional elements of the lysosome to form an integrated organelle and involves the synthesis, targeting, functional residence, and turnover of the proteins that comprise the lysosome. We have investigated lysosomal biogenesis during the formation and dissipation of storage vacuoles in two model systems. One involves the formation of sucrosomes in normal skin fibroblasts and the other utilizes storage disorder-affected skin fibroblasts; both of these systems result in an increase in the size and the number of lysosomal vacuoles. Lysosomal proteins, beta-hexosaminidase, alpha-mannosidase, N-acetylgalactosamine-4-sulfatase, acid phosphatase,

and the lysosome-associated membrane protein, LAMP-1, were shown to be elevated between 2- and 28-fold above normal during lysosomal storage. Levels of mRNA for the lysosome-associated membrane proteins LAMP-1 and LAMP-2, N-acetylgalactosamine-4-sulfatase, and the 46- and 300-kDa mannose-6-phosphate receptors were also elevated 2- to 8-fold. The up-regulation of protein and mRNA lagged 2-4 days behind the formation of lysosomal storage vacuoles. Correction of storage, in both systems, resulted in the rapid decline of the mRNA to basal levels, with a slower decrease in the levels of lysosomal proteins. Lysosomal biogenesis in storage disorders is shown to be a regulated process which is partially controlled at, or prior to, the level of mRNA. Although lysosomal proteins were differentially regulated, the coordination of these events in lysosomal biogenesis would suggest that a common mechanism(s) may be in operation.

PMID: 9223373 [PubMed - indexed for MEDLINE]

☐ **24:** Nippon Rinsho. 1995 Dec;53(12):3068-71. Related Articles, Links

[Lysosomal membrane transport disorders--cystinosis and sialic acid storage disorders (Salla disease, ISSD)]

[Article in Japanese]

Yano T, Ohno K.

Department of Neurobiology School of Life Science, Tottori University, Faculty of Medicine.

Cystinosis and sialic acid storage diseases (Salla disease, ISSD; infantile sialic acid storage disease) are lysosomal membrane disorders resulting from defective carrier-mediated transport of cystine and sialic acid across the lysosomal membrane. Both are rare autosomal recessively inherited disorders. The major clinical manifestations of cystinosis are renal failure and ocular damages. Sialic acid storage diseases are characterized by various degrees of psychomotor retardation. Salla disease patients trace a mild clinical course, and the life span is relatively long. While, in patients with ISSD follow a very severe progressive clinical course and often die in the first year of life. The genes responsible for each disease have not been isolated, the etiologies are not well known, and there is no specific treatment.

Publication Types:
- Review
- Review, Tutorial

PMID: 8577060 [PubMed - indexed for MEDLINE]

☐ **25:** Pediatr Pol. 1995 Oct;70(10):847-55. Related Articles, Links

[Thin-layer chromatography of urine oligosaccharides in diagnosis of some lysosomal storage disorders]

[Article in Polish]

Lugowska A, Tylki-Szymanska A, Sawnor-Korszynska D.

Zaklad Diagnostyki Laboratoryjnej Centrum Zdrowia Dziecka w Warszawie.

Inherited lysosomal storage disorders are caused by the deficiency or importantly lowered activity of one of the lysosomal enzymes, leading to the storage in the lysosomes the not degraded high-molecular substrates, among others: mucopolysaccharides, glycolipids, oligosaccharides and glycoproteins. Thin-layer chromatography of urine oligosaccharides allows reliable and fast diagnosis of some lysosomal storage disorders e.g. alpha-mannosidosis, fucosidosis, sialidosis, galactosialidosis, Schindler disease, GM1-gangliosidosis, GM2-gangliosidosis (Sandhoff type), Pompe disease, Salla disease, mucolipidosis II and III. We are presenting a modification of the Humbel and Collart's method of TLC of urine oligosaccharides. The principle of our modification is to introduce of the preliminary desalting step of the urine on the columns containing anionit BioRad AG 1 x 8 and cationit Dowex 50 x 8-200.

PMID: 8649932 [PubMed - indexed for MEDLINE]

☐ **26:** Am J Hum Genet. 1995 Oct;57(4):893-901. Related Articles, Links

Lysosomal free sialic acid storage disorders with different phenotypic presentations--infantile-form sialic acid storage disease and Salla disease--represent allelic disorders on 6q14-15.

Schleutker J, Leppanen P, Mansson JE, Erikson A, Weissenbach J, Peltonen L, Aula P.

Department of Medical Genetics, University of Turku, Finland.

Similarities in biochemical findings have suggested that Salla disease (SD) and the infantile form of sialic acid storage disease (ISSD) could represent allelic disorders, despite their drastically different clinical phenotypes. SD and ISSD are both characterized by lysosomal storage of free N-acetyl neuraminic acid. However, in SD the increase detected in urine is 8-24-fold, whereas in ISSD the corresponding amount is 20-50-fold and patients are also more severely affected. Here we report linkage studies in 50 Finnish SD families and 26 non-Finnish families with no genealogical connections to Finns affected either with the Finnish type of SD, the "intermediate" form of the disease, or ISSD. All forms of the disease show linkage to the same locus on 6q14-q15. Haplotype analyses of Finnish SD chromosomes revealed one common haplotype, which was also seen in most of the non-Finnish patients with Finnish type of SD. This ancestral haplotype deviated from those observed in ISSD patients, who had a different common haplotype.

PMID: 7573051 [PubMed - indexed for MEDLINE]

☐ **27:** J Inherit Metab Dis. 1995;18(6):717-22. Related Articles, Links

Elevated plasma chitotriosidase activity in various lysosomal storage disorders.

Guo Y, He W, Boer AM, Wevers RA, de Bruijn AM, Groener JE, Hollak CE, Aerts JM, Galjaard H, van Diggelen OP.

Department of Clinical Genetics, Erasmus University, Rotterdam, The Netherlands.

Recently a striking elevation of the activity of chitotriosidase, an endo beta-glucosaminidase distinct from lysozyme, was found in plasma from patients with Gaucher type I disease (McKusick 230800). Plasma chitotriosidase originates from activated macrophages and this elevation is secondary to the basic defect in Gaucher disease. To investigate the specificity of this phenomenon, we have investigated 24 different lysosomal storage diseases. In 11 different diseases increased chitotriosidase activity in plasma was found (in 28% of the patients). None of these diseases showed elevations as high as in Gaucher disease. Chitotriosidase was not significantly elevated in plasma from 20 different non-lysosomal enzymopathies or in plasma from patients with infectious diseases associated with hepatomegaly. The results show that marked elevation of chitotriosidase activity in plasma appears to be specific for Gaucher disease. The data further suggest that elevated levels of chitotriosidase activity in plasma from patients with unexplained diseases may be indicative for a lysosomal disorder.

PMID: 8750610 [PubMed - indexed for MEDLINE]

28: Southeast Asian J Trop Med Public Health. 1995;26 Suppl 1:54-8. Related Articles, Links

Lysosomal storage disorders in Thailand: the Siriraj experience.

Wasant P, Wattanaweeradej S, Raksadawan N, Kolodny EH.

Department of Pediatrics, Siriraj Hospital Medical School, Mahidol University, Bangkok, Thailand.

Lysosomal storage disorders are a heterogeneous group of biochemical genetic disorders; currently 40-50 are known. The clinical phenotype is determined by the tissue distribution of the storage material and degree of enzyme deficiency. The genetic transmission is mostly autosomal recessive. Lysosomal storage disorders can be divided into three groups according to the major organ system pathology: (1) Primary involvement of the central nervous system without significant somatic or skeletal pathology. Disorders of grey matter, eg gangliosidosis and disorders of white matter eg the leucodystrophy are the most common; (2) Primary involvement of the reticuloendothelial system with or without associated neuropathology, eg Niemann-Pick disease and Gaucher disease; (3) Multisystem involvement in which skeletal manifestations are prominent features. The mucopolysaccharidosis and mucolipidoses are the two major forms with this clinical phenotype. Lysosomal storage disorders identified at Siriraj Hospital are neuronal ceroid lipofuscinosis, GMI gangliosidosis, mucolipidosis II, Maroteaux-Lamy, sialidosis, Sly syndrome, Hunter syndrome, Morquio syndrome, Gaucher disease, Niemann-Pick, Sandhoff disease, Pompe's disease and many more. Most patients came from the provinces where consanguinity is common. Confirmation usually is done by enzyme assays using skin fibroblast culture or leucocytes. Genetic counseling is extremely important and prenatal diagnosis is recommended to high-risk couple.

Publication Types:
- Case Reports

PMID: 8629143 [PubMed - indexed for MEDLINE]

☐ **29:** Br Med Bull. 1995 Jan;51(1):106-22. Related Articles, Links

Gene therapy of lysosomal storage disorders.

Salvetti A, Heard JM, Danos O.

Retrovirus et Transfert Genetique, Institut Pasteur, Paris, France.

Lysosomal storage disorders (LSD) result from deficiencies in enzymes normally implicated in the catabolism of macromolecules inside the lysosome. Many of these enzymes can reach the lysosome after being secreted in the extracellular medium and recaptured by specific cell surface receptors. This has suggested a rationale for therapeutic approaches in LSD, in which the missing enzyme is provided by an external source. Current therapies based on this concept, including the administration of purified enzyme and bone marrow transplantation, have been shown to result in clinical improvements in both animal models and patients. Although considerable difficulties must be surmounted, LSD present a favourable situation for gene therapy. The gene corresponding to the affected enzyme has been identified in most diseases and cDNAs are available. Low and unregulated levels of enzyme activity should be sufficient for correction. Importantly, a variety of gene transfer strategies can be carefully evaluated in animal models.

Publication Types:
- Review
- Review, Academic

PMID: 7767637 [PubMed - indexed for MEDLINE]

☐ **30:** Biochim Biophys Acta. 1994 May 25;1226(2):138-44. Related Articles, Links

Free sphingoid bases in tissues from patients with type C Niemann-Pick disease and other lysosomal storage disorders.

Rodriguez-Lafrasse C, Rousson R, Pentchev PG, Louisot P, Vanier MT.

Department of Biochemistry, INSERM-CNRS 189, Lyon-Sud Medical School, Oullins, France.

The 20-fold increase of free sphingoid bases found in liver from a murine model of Niemann-Pick type C (NPC) combined to the NPC-like phenotype induced by addition of sphinganine to normal fibroblast cultures prompted us to investigate the potential involvement of these compounds in the human disease. The contents of sphingosine and sphinganine were measured in liver, spleen, brain and skin fibroblast cultures by a sensitive HPLC method. In liver and spleen from NPC patients, a 6- to 24-fold elevation of sphingosine and sphinganine already prominent at the fetal stage of the disease was observed, while no clear increase could be evidenced in brain tissue. A significant increase, not modulated by the intralysosomal content of free cholesterol, also occurred in skin

fibroblast cultures. To investigate the specificity of these findings, other lysosomal storage disorders were studied. A striking accumulation was found in liver and spleen (24- to 36-fold) from patients with Niemann-Pick disease type A and B (sphingomyelinase-deficient forms), and in cerebral cortex of type A Niemann-Pick disease. A significant storage also occurred in Sandhoff disease, while several other sphingolipidoses showed a moderate elevation. In all cases but Sandhoff disease brain, the sphingosine/sphinganine ratio remained unchanged, suggesting that the accumulated free sphingoid bases derived from sphingolipid catabolism. Formation of complexes between sphingosine and the lipid material accumulated in lysosomes might be a general mechanism in lysosomal lipidoses. In NPC, however, an increase of free sphingoid bases disproportionate to the degree of lysosomal storage and a specific involvement of cultured fibroblasts suggested a more complex or combined mechanism.

PMID: 8204660 [PubMed - indexed for MEDLINE]

31: Biol Cell. 1994;81(2):143-52. Related Articles, Links

Effects of suramin, a polyanionic drug inducing lysosomal storage disorders on tooth germs in vitro.

Gritli-Linde A, Ruch JV, Mark MP, Lecolle S, Goldberg M.

Laboratoire de Biologie et Biomateriaux du Milieu Buccal et Osseux, Faculte de Chirurgie Dentaire LA 1505, Montrouge, France.

Suramin, a potent inhibitor of lysosomal enzymes, is commonly employed as a tool for inducing experimental mucopolysaccharidosis and lipidosis. The effects of the drug on embryonic mouse molars were analysed. Presecretory ameloblasts and odontoblasts were loaded with lysosome-like vacuoles. Staining with MC22-33F, an antibody to choline phospholipids and sphingomyelin, was completely reversed in the suramin-treated germs, in that it stained only presecretory ameloblasts (versus odontoblasts and some pulpal cells in the control group), according to a developmentally regulated pattern. The suramin-induced cytoplasmic changes were reminiscent of the features of mucopolysaccharidoses and lipidoses. The basement membrane, separating the enamel organ from the dental papilla, displayed suramin-induced patches, and in predentin collagen fibrillogenesis was found to be disturbed. Furthermore, autoradiography was employed to reveal uptake and distribution of [3H] suramin in the cells and predentin. Finally, a suramin-induced disturbance of the metabolism of sulphated macromolecules was found. The results imply that suramin effects in vitro on tooth germs can be used as a useful experimental model with to study both the action of the drug as well as cell and extracellular matrix perturbations in a mucopolysaccharidosis-like condition.

PMID: 7849606 [PubMed - indexed for MEDLINE]

32: Nippon Rinsho. 1993 Sep;51(9):2264-8. Related Articles, Links

[Lysosomal storage disease: a group of genetic neurodegenerative disorders]

[Article in Japanese]

Suzuki Y.

Tokyo Metropolitan Institute of Medical Science.

Lysosomal storage disease is a group of neurometabolic diseases mainly occurring in infancy and childhood. They were first recognized as new diseases on the basis of unique clinical manifestations or pathological findings, and then the stage of biochemical analysis of storage material and enzyme assays in tissues and cells from patients followed. Recent technological development has enabled us to look further into the molecular genetic basis of these inherited diseases. Protein analysis revealed intracellular events of the mutant enzyme molecule responsible for the pathogenesis of a disease, and more detailed information has been obtained about the mutant gene and its product. Clinical manifestations are not always uniform for a single disease with mutations in the same gene. Clinical subtypes have been proposed for many lysosomal diseases. At present, the molecular and metabolic basis of each phenotypic expression is not clear, although common mutations have been found for specific clinical forms in some diseases. In this article, the current status of lysosomal disease research was summarized, particularly focusing on molecular pathology and molecular diagnosis. Finally future prospects for pathogenetic analysis of neural dysfunction and possible gene therapy were briefly discussed.

Publication Types:
- Review
- Review Literature

PMID: 8411700 [PubMed - indexed for MEDLINE]

☐ **33:** J Inherit Metab Dis. 1993;16(2):288-91. Related Articles, Links

Pathogenesis of lysosomal storage disorders as illustrated by Gaucher disease.

Aerts JM, Van Weely S, Boot R, Hollak CE, Tager JM.

E.C. Slater Institute for Biochemical Research, University of Amsterdam, The Netherlands.

Publication Types:
- Review
- Review, Tutorial

PMID: 8411983 [PubMed - indexed for MEDLINE]

☐ **34:** C R Seances Soc Biol Fil. 1993;187(5):596-607. Related Articles, Links

[Lysosomal storage diseases, genetic or drug-induced? effect of glycosaminoglycan and sphingolipid disorders on dental tissues]

[Article in French]

Goldberg M, Gritli A, Bloch-Zupan A, Septier D, Lecolle S, Legrand JM, Ruch JV.

Laboratoire de Biologie et Biomateriaux du Milieu Buccal et Osseux, Faculte de Chirurgie Dentaire, Paris V, Montrouge, France.

In vivo studies were carried out on dental tissues of rat incisor after a single injection of suramin, a drug which induces mucopolysaccharidosis-like disease. Accumulation of lysosome-like structures was seen in secretory ameloblasts and odontoblasts. In vitro studies on embryonic tooth germ buds showed similar changes when they were cultured in presence of suramin. Anti-phospholipid immunolabelling revealed a developmentally regulated temporo-spatial pattern. Radiolabeling with 3H-suramin indicated cytosolic and nuclear incorporation. The drug acting as polyanion interacted directly with predentine. 35S sulphate incorporation was impaired by the drug. Another lysosomal storage disease, the sphingolipidosis, Krabbe's disease was also investigated in human. Changes were observed in pulp cells and as a consequence in dentin. Enamel also displayed many changes. Pharmacological or genetically acquired diseases constitute models providing insights on the role played by glycosaminoglycans and phospholipids in biomineralization.

PMID: 8069712 [PubMed - indexed for MEDLINE]

☐ **35:** Clin Neuropathol. 1992 Sep-Oct;11(5):251-5. Related Articles, Links

Neuronal ubiquitin and neurofilament expression in different lysosomal storage disorders.

Zhan SS, Beyreuther K, Schmitt HP.

Institute of Neuropathology, University of Heidelberg, Germany.

We studied various lysosomal storage disorders such as Tay-Sachs' disease, Niemann-Pick's disease, and Hunter's disease for their immunoreactivity with antibodies against ubiquitin (Ub) and neurofilaments (NF). We found that in all cases, irrespective of the nature of the storage material or disorder, only a minor proportion of neurons (20-30% at most), as a rule, moderately reacted with the Ub antibody, while the majority of the distended neurons neither expressed Ub nor NF epitopes. These findings suggest that the UB dependent proteolytic pathway may play a secondary role in the lysosomal storage disorders, at least in the advanced stages which are observed at autopsy. It seems that the Ub expression of a minor proportion of neurons should be regarded as an unspecific epiphenomenon rather than as a mechanism of major significance in the basic metabolism of these disorders, in which the inclusions consist of membrane-bound lipid material.

PMID: 1385029 [PubMed - indexed for MEDLINE]

☐ **36:** FASEB J. 1991 Mar 1;5(3):301-8. Related Articles, Links

Saposin proteins: structure, function, and role in human lysosomal storage disorders.

O'Brien JS, Kishimoto Y.

Department of Neurosciences, University of California, San Diego, La Jolla 92093.

Saposins are sphingolipid activator proteins, four of which are derived from a single precursor, prosaposin, by proteolytic processing. These small heat-stable glycoproteins (12-14 kDa) are required for the lysosomal hydrolysis of a variety of sphingolipids. Characterization of these four activator proteins, two of which were recently discovered, and their importance in human health and disease are reviewed in this article.

Publication Types:
- Review
- Review, Academic

PMID: 2001789 [PubMed - indexed for MEDLINE]

☐ **37:** In Vitro Cell Dev Biol. 1988 Dec;24(12):1159-64. Related Articles, Links

Culture conditions found to minimize false positive diagnosis of lysosomal storage disorders.

Arnon J, Ornoy A, Bach G.

Dept. of Anatomy and Embryology, Hadassah Medical School; Jerusalem, Israel.

The effect of culture conditions on the ultrastructure and enzyme activities of cultured skin fibroblast cells relevant to the diagnosis of lysosomal storage disorders are reported. The parameters examined were: pH of the culture media, type of media, increasing cell passage, and day of harvest. Ultrastructural changes were defined in terms of the number of lysosome-like inclusion bodies per cell according to a method devised in our laboratory and proven reliable in the detection of affected individuals. Our biochemical results included determination of enzyme activities of beta-hexosaminidase, alpha-mannosidase, beta-glucuronidase-lysosomal enzymes, arylsulfatase C, a microsomal marker, and 5' nucleotidase, a plasma membrane marker. Our results indicate that the cellular ultrastructure is more sensitive than enzyme activity to changes in culture conditions. The resulting ultrastructural "artifacts" observed under certain conditions were severe enough to result in a mistaken diagnosis. Due to certain difficulties we had previously encountered in heterozygote cultures (for lysosomal storage disorders) of amniotic cells, we decided to examine heterozygote cultures of skin fibroblasts. From these (preliminary) studies it seems that an elevation in the pH over the physiologic levels in the culture media may help to define between normal individuals and affected heterozygotes. On the basis of our results, we recommend that to minimize false positive ultrastructural results for the diagnosis of lysosomal storage disorders, cultures be grown in minimal essential medium, the pH of the medium carefully monitored to remain below 7.4, examining the cultures not later than cell Passage 8 and no later than Day 10 after subculture.

PMID: 3209585 [PubMed - indexed for MEDLINE]

☐ **38:** Am J Hum Genet. 1988 Feb;42(2):271-3. Related Articles, Links

Selection in favor of lysosomal storage disorders?

Zlotogora J, Zeigler M, Bach G.

Department of Human Genetics, Hadassah University Hospital, Jerusalem, Israel.

Four examples of Israeli communities or large families in which high consanguinity is common are presented, with two different lysosomal storage disorders within each community. In each of the four cases the stored substances share common chemical structure, despite the different lysosomal hydrolases involved in each disease. A similar phenomenon is known among the Ashkenazi Jews, in whom four of the most frequent hereditary disorders are lysosomal storage disorders, which are characterized by storage of sphingolipid derivatives. Similar findings are reported in the literature in other communities. We suggest that this phenomenon indicates a selection in favor of lysosomal storage disorders of similar nature in certain populations. The selection forces leading to this phenomenon have not been identified yet, and it has not yet been determined whether these forces are the same in the different communities presented here.

Publication Types:
- Case Reports

PMID: 3124612 [PubMed - indexed for MEDLINE]

39: Trans Am Ophthalmol Soc. 1987;85:471-97. Related Articles, Links

The efficacy of conjunctival biopsy as a screening technique in lysosomal storage disorders.

Mazow ML.

Publication Types:
- Review
- Review of Reported Cases

PMID: 3328919 [PubMed - indexed for MEDLINE]

40: Prenat Diagn. 1986 Sep-Oct;6(5):351-61. Related Articles, Links

Cultured amniotic fluid cells for prenatal diagnosis of lysosomal storage disorders: a methodological study.

Arnon J, Ornoy A, Bach G.

The influence of culture conditions on the ultrastructure and enzyme activities of amniotic fluid cells are reported. Morphological changes were determined as a function of the number of lysosomal-like inclusion bodies per cell, and these results correlated to the activity of beta-hexosaminidase, alpha-mannosidase, beta-glucuronidase, arylsulphatase C and 5' nucleotidase. The parameters examined were pH of the culture media, type of media, increasing cell passage and day of harvest. Our results indicate that enzyme activities are

less sensitive to changes in culture conditions as compared to ultrastructural changes. We therefore recommend that in order to obtain reliable ultrastructural results for the diagnosis of storage disorders, cultures should be grown in MEM as the culture medium, the pH of the medium carefully monitored to remain below pH 7.4, examining the cultures no later than the eighth cell passage and no later than the 10th day after subculture.

PMID: 3022278 [PubMed - indexed for MEDLINE]

41: Hum Genet. 1986 Jul;73(3):214-7. Related Articles, Links

Free N-acetylneuraminic acid (NANA) storage disorders: evidence for defective NANA transport across the lysosomal membrane.

Mancini GM, Verheijen FW, Galjaard H.

To study the biochemical defect underlying N-acetylneuraminic acid (NANA) storage disorders (NSD), a tritium-labeled NANA-methylester was prepared and its metabolism was studied in normal and mutant human fibroblasts. The uptake of methylester, its conversion into free NANA, and the release of free NANA was studied in lysosome-enriched fractions. In three clinically different types of NSD accumulation of free NANA was observed and the half-life of this compound was significantly increased. Our observations indicate the existence of a transport system for NANA across the lysosomal membrane, which is deficient in all variants of NSD.

PMID: 3733077 [PubMed - indexed for MEDLINE]

42: Lancet. 1985 Dec 7;2(8467):1296. Related Articles, Links

Pseudodeficiencies in lysosomal storage disorders.

Zlotogora J, Bach G.

Publication Types:
- Letter

PMID: 2866352 [PubMed - indexed for MEDLINE]

43: Med J Aust. 1984 Feb 18;140(4):188-9. Related Articles, Links

Diagnosis of lysosomal storage disorders.

Kerr C.

PMID: 6694619 [PubMed - indexed for MEDLINE]

☐ **44:** Virchows Arch B Cell Pathol Incl Mol Pathol. 1984;46(1-2):13-9. Related Articles, Links

Ito cells in lysosomal storage disorders. An ultrastructural study.

Elleder M.

An ultrastructural study was performed in a series of liver biopsies from patients with various lysosomal storage diseases to evaluate the extent of lysosomal hypertrophy and hyperplasia in Ito cells (ICs). In previous studies this has been considered to be absent or only rudimentary. Lysosomal storage was recognized by the presence of storage cytosomes surrounded by limiting membranes and by the appearance of their content which was identical to that in other hepatic storage lysosomes. Storage was found in sphingomyelinase deficiency (Niemann-Pick disease types A, B), in Wolman's disease, GM1 gangliosidosis, mucopolysaccharidosis and in multiple sulphatase deficiency. In type C Niemann-Pick disease it was virtually absent with the exception of cases with prominent hepatic symptomatology. Storage was of variable degree and was accompanied by a decrease in the physiological fat content (cytoplasmic lipid droplets). The degree to which ICs were affected correlated only with the extent to which nonspecific fibroblasts were involved in the specimens studied and thus seems to reflect storage in the fibroblastic population.

PMID: 6147922 [PubMed - indexed for MEDLINE]

☐ **45:** Anal Biochem. 1980 Feb;102(1):213-9. Related Articles, Links

High-performance liquid chromatographic analysis of oligosaccharides and glycopeptides accumulating in lysosomal storage disorders.

Kin NM, Wolfe LS.

PMID: 6766687 [PubMed - indexed for MEDLINE]

☐ **46:** Front Biol. 1979;48:49-130. Related Articles, Links

Drug-induced lysosomal storage disorders.

Lullmann-Rauch R.

Publication Types:
- Review

PMID: 387466 [PubMed - indexed for MEDLINE]

☐ **47:** Birth Defects Orig Artic Ser. 1976;12(3):1-13. Related Articles, Links

Chemical diagnosis of inborn lysosomal storage disorders involving the eye.

Dawson G, Tsay GC.

Publication Types:
- Review

PMID: 821555 [PubMed - indexed for MEDLINE]

48: Arch Neurol. 1975 Sep;32(9):592-9. Related Articles, Links

Lysosomal storage disorders. Diagnosis by ultrastructural examination of skin biopsy specimens.

O'Brien JS, Bernett J, Veath ML, Paa D.

Fifteen patients with lysosomal storage diseases were studied. Diagnoses of their illnesses included infantile Gaucher disease; Krabbe disease; Niemann-Pick disease, type A; glycogen storage disease, type 3; Fabry disease, Jansky-Bielschowsky and Spielmeyer-Vogt types of amaurotic idiocy, GM1 gangliosidosis, type 1; Hurler disease; and Sanfilippo disease, types A and B. We carried out ultrastructural examinations of skin biopsy specimens that were taken to establish a cultured fibroblast line on each patient. We found diagnostic storage inclusions in all patients except those with infantile Gaucher disease, Krabbe disease, and Spielmeyer-Vogt disease, This technique can be carried out on a specimen obtained by a primary physician on an out-patient basis, thus avoiding major surgery.

PMID: 809024 [PubMed - indexed for MEDLINE]

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